

## **St. Jude Clinical Genomics Germline Variant Investigation Process**

### **Overview**

Variants detected in the Clinical Genomics laboratory at St. Jude Children's Research Hospital go through a multi-faceted evaluation by a PhD-level variant scientist, followed by a review by a Clinical Genomics Committee which is comprised of pathologists, oncologists, genetic counselors, and computational biologists. St. Jude Clinical Genomics provides a summary of the evidence as well as an overall interpretation of the clinical significance of the detected variant(s) in the patient's report.

Germline variant classification at St. Jude Children's Research Hospital is primarily based on the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) variant classification guidelines (Richards et al 2015, PMID: 25741868) and subsequent ClinGen Sequence Variant Interpretation recommendations (<https://clinicalgenome.org/curation-activities/variant-pathogenicity/documents/>), in conjunction with internal panel review. Variants in genes with ClinGen Expert Panel specifications for variant interpretation will be curated and interpreted in accordance with these published specifications, in conjunction with internal panel review. For genes that do not yet have ClinGen Expert Panel specifications for variant classification, the ACMG/AMP (2015) guidelines will provide the basis of classification and the final pathogenicity classification will be determined by a germline review panel following presentation of evidence by the variant scientist(s). Variants will be placed into the recommended five classification categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

### **St. Jude Modifications to ACMG Guidelines Used for Variant Classification**

Our germline review committee aims to increase consistency by clarifying, and where possible, quantifying sections of the ACMG guidelines that are ambiguous.

- Variants in genes with established prevalence and penetrance estimates for the corresponding phenotype may be called likely benign based on BS1 alone.
- St. Jude may will extend ACMG guidelines to incorporate relevant data that are currently not captured (e.g. somatic data such as 'second hits' in the tumor or loss of heterozygosity, high mutational burden, tumor signature, and transcriptome data).
- Additional lines of evidence may be used that are disorder- or gene-specific. This will be detailed in the variant description.

**Updated: 9/30/2020**